Treatment of non-traumatic osteonecrosis with endogenous Mesenchymal stem cells

Grant Award Details

Treatment of non-traumatic osteonecrosis with endogenous Mesenchymal stem cells

Grant Type: Disease Team Therapy Development - Research

Grant Number: DR2A-05302

Project Objective: To develop cGMP LLP2A-Alendronate (LLP2A-Ale) for bone regeneration and conduct a Phase 1a/1b trial for osteonecrosis (post-CDAP indication change from osteoporosis --> osteonecrosis in October 2013.)

Investigator:

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Type:	PI

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Institution:	University of California, Davis
Type:	Co-PI

Disease Focus: Bone or Cartilage Disease, Osteonecrosis

Human Stem Cell Use: Adult Stem Cell

Award Value: $19,999,867

Status: Active

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Grant Application Details

Application Title: Treatment of osteoporosis with endogenous Mesenchymal stem cells

Public Abstract: Although most individuals are aware that osteoporosis is disease of increased bone fragility that results from estrogen deficiency and aging, most are unaware of the high risk and cost of the disorder. It is estimated that close to 30% of the fractures that occur in the United States each year are due to osteoporosis (Schwartz & Kagan 2002). California, with one of the largest over-age-65 populations, is expected to double the fracture rate from 1995 to 2015 (Schwartz & Kagan 2002). Current treatment of osteoporosis is focused on anti-resorptive agents that prevent further bone loss. These agents and are effective in reducing new vertebral fractures but less effective for the prevention of hip fractures, and the duration of use of one anti-resorptive class, the bisphosphonates, is limited due to a concern about weakening of the cortical bone with longterm use. The only bone growing agent that is approved by FDA is the protein, hPTH 1-34, which requires two years of daily injections, is only approved by the FDA for one course of treatment, is only effective in about 60% of treated individuals for reduction of vertebral fractures, and has not been shown to be effective in reducing new hip fractures. This leaves an unmet medical need for an anabolic or agent that stimulates bone formation for millions of elderly Californians that suffer or will suffer from this disease.

We have developed a small molecule, LLP2A-Ale that directs endogenous mesenchymal stem cells (MSCs), the cells that have the potential to grow bone tissue, to the bone surface to form new bone. We propose a development plan for this small molecule, LLP2A-Ale for the treatment of osteoporosis in both postmenopausal women and men.

Yrs. 1-2: These 2 years will be spent with optimizing the manufacturing and packaging of the small molecule, obtaining information about the efficacy and toxicity in preclinical models, and preparing documents for an FDA meeting when the preclinical studies are completed to provide comment on the proposed Phase I clinical trials.

Yrs. 3-4. We plan perform a Phase I study with two parts. Part I will study postmenopausal women with osteopenia and a fracture risk (3% for hip fracture and 20% for major nonvertebral fractures over the next 10 years). After the initial Phase I study in postmenopausal women we will perform Part 2 and study both postmenopausal women and men with similar inclusion and exclusion criteria. The primary endpoint of these studies will be change in biochemical markers of bone turnover (PINP, BSAP, osteocalcin), and secondary endpoints will be bone mineral density of the lumbar spine measured by DXA and trabecular bone volume measured by QCT. The Phase I trials will also include required pharmacokinetic and pharmacodynamic measures to obtain information about the action of this small molecule and to inform us for Phase II clinical studies in the future.

Statement of Benefit to California:

Osteoporosis is a disease of the elderly that results from a process of age related bone loss that renders the bone fragile. Current osteoporosis treatments have relatively good efficacy in reducing incident fractures. However these agents (anti-resorptive agents or the anabolic agent rhPTH (1-34) only reduce the risk of vertebral fractures about 60%, and hip fractures only 40%, and these agents require years of treatment to be effective. The goal of this project is to increase bone homing of the endogenous MSCs with a small molecule (LLP2A-Ale) to form new bone as a novel treatment for osteoporosis that could cure osteoporosis with only 3-4 injections by mobilizing the endogenous MSCs to build bone. Our molecule would be highly competitive in this market as the efficacy of increasing bone mass and bone strength would be high and the risks in a very acceptable range.

The market potential for bone tissue regeneration is large as it is estimated that close to 1/3 of fractures that occur in the US each year are due to osteoporosis (Schwartz & Kagan (2002). California, with one of the largest over-age-65 populations, is expected to double the fracture rate from 1995 to 2015 (Schwartz & Kagan 2002). One study places the cost per year in osteoporotic fractures at 2.4 billion dollars (Schwartz & Kagan 2002), establishing it as one of the highest health care costs for older individuals. The prevalence of osteoporosis is projected to increase with increasing lifespan globally both from age related bone loss and from secondary causes of bone loss including inflammatory diseases and cancer. The market potential for bone tissue regeneration is large, an estimated 2 million fractures and $19 billion in costs annually. By 2025, experts predict that osteoporosis will be responsible for approximately 3 million fractures and $25.3 billion in costs each year (publication from National Osteoporosis Foundation). The osteoporotic patients spend about $10 a month for the generic version of Fosamax, at the lower end, to about $80 a month for brand-name Fosamax or Actonel to $900 or more a month for Forteo (rhPTH (1-34).

Therefore, once validated in osteoporosis patients, this form of tissue regeneration would be effective in patients with primary osteoporosis, in patients with secondary osteoporosis due to long term glucocorticoid treatment or after chemotherapy in both men and women and to augment peak bone mass in children in whom current osteoporosis medications are contraindicated, in individuals who have had radiation to their skeletons in whom rhPTH (1-34) is contraindicated and to augment fracture healing in the elderly. Our agent would have the potential to save the State of California millions of dollars in health care and would allow these osteoporotic individuals to live longer and be independent longer.
